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Cholinergic modulation of the cerebral metabolic response to citalopram in Alzheimer's disease

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Abstract

Pre-clinical and human neuropharmacological evidence suggests a role of cholinergic modulation of monoamines as a pathophysiological and therapeutic mechanism in Alzheimer's disease. The present study measured the effects of treatment with the cholinesterase inhibitor and nicotinic receptor modulator, galantamine, on the cerebral metabolic response to the selective serotonin reuptake inhibitor, citalopram. Seven probable Alzheimer's disease patients and seven demographically comparable controls underwent two positron emission tomography (PET) glucose metabolism scans, after administration of a saline placebo infusion (Day 1) and after citalopram (40 mg, IV, Day 2). The scan protocol was repeated in the Alzheimer's disease patients 2 months after titration to a 24 mg galantamine dose. At baseline, cerebral glucose metabolism was reduced in Alzheimer's disease patients relative to controls in right middle temporal, left posterior cingulate and parietal cortices (precuneus and inferior parietal lobule), as expected. Both groups demonstrated acute decreases in cerebral glucose metabolism after citalopram to a greater extent in the Alzheimer's disease patients. In the patients, relative to the controls, citalopram decreased glucose metabolism to a greater extent in middle frontal gyrus (bilaterally), left middle temporal gyrus and right posterior cingulate prior to treatment. Galantamine treatment alone increased metabolism in the right precuneus, right inferior parietal lobule and right middle occipital gyrus. In contrast, during galantamine treatment, citalopram increased metabolism in the right middle frontal gyrus, right post-central gyrus, right superior and middle temporal gyrus and right cerebellum. The combined cerebral metabolic effects of galantamine and citalopram suggest, consistent with preclinical data, a synergistic interaction of cholinergic and serotonergic systems.

Keywords: Alzheimer's disease; positron emission tomography (PET); acetylcholine; serotonin; citalopram; galantamine

Abbreviations: ADAS-COG = Alzheimer's disease Assessment Scale score; MCI = mild cognitive impairment; MMSE = mini mental status examination; NPI = Neuropsychiatric Inventory; PET = positron emission tomography

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Introduction

The pre-synaptic cholinergic deficit has been a major focus of research and treatment development in Alzheimer's disease (Davies and Maloney, 1976). Deficits in other neurotransmitters, including monoamine systems (dopamine, serotonin and norepinephrine) have been reported, as well (Palmer and DeKosky, 1993). In particular, serotonergic deficits (decrease in transporters and 5-HT1A and 5-HT2A receptors), as shown by neuropathological and neuroimaging studies, have been shown to be greater and more widespread than other neurotransmitter deficits in Alzheimer's disease, including other monoaminergic and muscarinic cholinergic systems and have also been observed in mild cognitive impairment (MCI, as reviewed by Cross *et al*., 1986; Nazrali and Reynolds, 1992; Meltzer *et al*., 1998; Hasselbalch *et al*., 2008).

Monoamine systems are of particular interest as these systems are neuroanatomically and functionally linked to acetylcholine, are affected in Alzheimer's disease and have been implicated in behavioural symptoms (such as depression, agitation, psychosis). Cholinergic agents, including cholinesterase inhibitors and nicotinic receptor agonists, as well as lesions of the basal forebrain cholinergic system, have been shown to affect monoamine concentrations (Smith, 1988; Giacobini *et al*., 1996; Maelicke *et al*., 2000). The observation in some studies that the cholinesterase inhibitors may improve behavioural symptoms in Alzheimer's disease that may be related to alterations in monoamine systems suggests that the study of synergistic interactions between cholinergic and monoaminergic systems may have mechanistic and therapeutic relevance (Cummings and Kaufer, 1996). Several lines of evidence suggest that interactions between cholinergic and serotonergic systems may be particularly relevant to Alzheimer's disease. Cholinergic modulation of serotonin has been demonstrated by neuroanatomic and neurochemical methods in cortical and limbic regions, in addition to the synergistic role of the two systems in memory function (Azmitia and Segal, 1978; Vanderwolf, 1987; Nilsson *et al*., 1992; Little *et al*., 1995). Animal models of cholinergic hypofunction (lesion of the nucleus basalis of Meynert) have demonstrated acute decreases in 5-HT1A and 5-HT2A receptor binding and chronic increases in 5-HT2A receptor binding over time (Quirion *et al*., 1985; Quirion and Richard, 1987). Decreases in serotonin concentrations and receptors and (to a greater extent) ratios of serotonergic to cholinergic postmortem neurochemical measures have been associated with cognitive impairment, rate of cognitive decline and behavioural symptoms in Alzheimer's disease, indicating that dysfunction of both systems is related to greater symptomatology (Palmer *et al*., 1988; Garcia-Alloza *et al*., 2005). Combined administration of cholinergic and serotonergic antagonists or synthesis inhibitors produced greater cognitive deficits than administration of either compound alone (Vanderwolf, 1987; Little *et al*., 1995). Combined enhancement of cholinergic and serotonergic function has shown relative greater improvements in memory (Altman *et al*., 1987).

The purpose of the present study was to evaluate whether chronic treatment with cholinesterase inhibitors would affect the cerebral metabolic response to citalopram in Alzheimer's disease patients. Galantamine was the cholinesterase inhibitor chosen for use in the study because it is an effective and well-tolerated medication (Raskind *et al*., 2000; Tariot *et al*., 2000). Galantamine is a competitive and reversible inhibitor of acetylcholinesterase that also allosterically modulates the nicotinic acetylcholine receptor (Thomsen and Kewitz, 1990; Schrattenholz *et al*., 1996). The dual mechanisms of action might result in a greater net effect on serotonin systems (as well as other monoamine systems) as compared with cholinesterase inhibitors with a single mechanism of action. The acute cerebral metabolic response to the selective serotonin reuptake inhibitor (SSRI), citalopram was measured as has been done in previous studies (Smith *et al*., 2002a, b). Citalopram was chosen as it is the most pharmacoloigically selective of the SSRI's, is available in intravenous form and is well tolerated in individuals across the lifespan (Goldberg *et al*., 2004). To measure the dynamic response of the serotonin system, the most direct method would be to measure changes in serotonin receptor availability secondary to a pharmacologic increase in serotonin using a similar paradigm as has been developed for the dopamine system (Dewey *et al*., 1993). As has been reviewed previously (Smith *et al*., 2002a, b), the available serotonin receptor radiotracers do not show an interpretable changes in specific binding associated with a pharmacologic increase in serotonin. Thus, the combination of the glucose metabolism measures with acute intravenous administration of citalopram was used as a measure of the functional response to acute serotonin transporter occupancy (>70%; Hinz *et al*., 2008) and a secondary, pharmacologic increase in serotonin (Kreiss *et al*., 1993). The paired positron emission tomography (PET) scans were performed in the Alzheimer's disease patients before and during treatment with galantamine and in the control subjects on one occasion. There were two aims of the study. *Aim 1* was to compare the cerebral metabolic response to citalopram in Alzheimer's disease patients relative to controls. The hypothesis was tested that the cerebral metabolic response to citalopram would be greater in Alzheimer's disease patients relative to controls. *Aim 2* was to compare the cerebral metabolic response to citalopram in the Alzheimer's disease patients before and during galantamine treatment. The hypothesis was tested that the cerebral metabolic response to citalopram in the Alzheimer's disease patients would be enhanced by galantamine treatment, due to the synergistic interaction between the cholinergic and serotonergic systems shown in preclinical studies.

Materials and methods

Alzheimer's disease patients and controls underwent medical (including laboratory testing and toxicology screening), psychiatric evaluation (SCID) and MRI (GE 1.5T Magnetom Vision). Subjects were excluded based upon a history of or current significant medical (including insulin dependent diabetes), psychiatric (DSM-IV axis I psychiatric disorder) or neurological disorder (except for Alzheimer's disease in the patients), substance abuse or use of prescription or over the counter medications with central nervous system effects (including cholinesterase inhibitors, antihistamines, cold medications) within the past month. Seven patients who met DSM-IV and National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related

Disorders Association criteria (McKhann *et al.*, 1984) for probable Alzheimer's disease were enrolled in the study (mean age 76.3 ± 11.1 years, two males/five females, education 14.6 ± 2.8, mini mental status examination [MMSE; Folstein *et al.*, 1975) score 23.4 ± 1.9]. The total Alzheimer's disease Assessment Scale score (ADAS-COG, long form; Rosen *et al.*, 1984) was 19.3 ± 7.2. The total Neuropsychiatric Inventory (NPI; Cummings *et al.*, 1994) score at baseline was 7.7 ± 10.9. Six of the seven patients had never been treated with a cholinesterase inhibitor. Seven healthy controls were recruited from the community and enrolled in the study (mean age 71.9 ± 6.2 years, two males/five females, education 14.0 ± 2.5, MMSE score 29.1 ± 0.9). After a complete description of the study to the subjects, written informed consent was obtained according to procedures established by the Institutional Review Board and the Radiation Safety Committee of the North Shore-Long Island Jewish Health System.

To address Aim 1 of the study, controls and Alzheimer's disease patients underwent one PET scan session to measure the cerebral metabolic effects of citalopram. To address Aim 2 of the study, galantamine treatment began in the Alzheimer's disease patients after the baseline PET scan session and the PET scans were repeated after 8 weeks of treatment at the highest galantamine dose (week 16). The treatment protocol involved 4 weeks of administration of galantamine at a dose of 8 mg per day, followed by 4 weeks at 16 mg and then an increase to 24 mg, if clinically indicated as in previous clinical trials (Raskind *et al.*, 2000; Tariot *et al.*, 2000). All patients tolerated the galantamine well and were titrated to the 24 mg dose of galantamine. Subjects were treated for an additional 2 months after the second PET scan session on the 24 mg dose for a total of 24 weeks (4 months at the 24 mg dose). The clinical and neuropsychological assessments performed at the time of the two PET scan sessions (week 16) and the end of the treatment study included the MMSE, NPI, Clinician's Interview-Based Impression of Change plus Caregiver Input (CIBIC-plus; Schneider *et al.*, 1997) and the ADAS-COG. The clinical and neuropsychological data were analysed using repeated measures analysis of variance (ANOVA).

Serum and plasma samples for assays of citalopram levels and prolactin concentrations, respectively, were obtained at pre-determined intervals (pre-infusion, end of infusion and 15, 30 60, 90, 120 min post-infusion). Prolactin concentrations were measured to evaluate the effects of citalopram administration on the serotonin system independently of the glucose metabolism measures. The acute increase in prolactin after a pharmacologic increase in serotonin has been reported to reflect an activation of post synaptic, hypothalamic serotonin receptors (5-HT1A, 5-HT2A and 5-HT2C subtypes; Raap and Van de Kar, 1999). The assays were performed in the Geriatric Psychopharmacology Laboratory, Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine (Smith *et al.*, 2002a, b). The ELISA measurements for citalopram and prolactin have been described in an earlier publication (Smith *et al.*, 2002a, b). The prolactin assay is linear from 2.0 to 180 ng/ml, which is within the range of values obtained. Intra-assay precision of 16 replicates ranged from 7.8% to 8.2% with inter-assay precision of 16 replicates of 6.7–10.4%. The inter-assay coefficient of variation for citalopram is (2.9% at 15 ng/ml and 1.8% at 220 ng/ml, which is also within the range of values obtained (Foglia *et al.*, 1997).

The data for citalopram and prolactin concentrations were analysed as areas under the curve (AUC increase from baseline, calculated using standard trapezoidal methods). The values were expressed as AUCs to integrate the data within the time frame of the PET scans, and because the main effects of time and group in the statistical analyses for both the AUC and individual time points were non-significant. For the comparison of Alzheimer's disease patients to controls, the drug levels and prolactin data were analysed using repeated measures analysis of variance with diagnosis (control/Alzheimer's disease patient) as a between subject factor and condition (two levels: placebo/citalopram) as a within subject factor. For the galantamine comparison in the Alzheimer's disease patients, the drug levels and prolactin data were analysed using repeated measures analysis of variance with drug (baseline/galantamine) as a between subject factor and condition (two levels: placebo/citalopram) as a within subject factor.

The PET scans were performed using a GE Advance Tomograph in the Center for Neurosciences, the Feinstein Institute for Medical Research (Smith *et al.*, 2002a, b). The subjects underwent intravenous infusions of placebo (250 ml of saline) or citalopram (40 mg of the drug diluted in 250 ml saline) over 60 min on two consecutive days. The order of placebo-drug administration was not randomized. The study was conducted as 'single blind' in that subjects were informed that they will receive either citalopram or placebo prior to each of the scans 30 min after the end of the infusion of placebo/citalopram, 5 mCi of [18F]-fluorodeoxyglucose ([18F]-FDG) was injected as an intravenous bolus. During radiotracer uptake, subjects were maintained in a quiet, darkened room with eyes open and ears unoccluded. Subjects were positioned in the scanner. First, a 10-min transmission scan and a 5-min twodimensional emission scan were acquired for photon attenuation correction. Then, a threedimensional emission scan began at 35 min after radiotracer injection and lasted for 10 min.

Glucose metabolic rates were calculated (in ml/100 g/min) on a voxel-by-voxel basis (Takikawa *et al.*, 1993; Smith *et al.*, 2002a, b). PET data processing was performed on the quantitative glucose metabolism images using the statistical parametric mapping program (SPM99; Friston *et al.*, 1995). The images were smoothed with an isotropic Gaussian kernel (FWHM 8 mm for all directions). The glucose metabolic rates were normalized by scaling to a common mean value across all scans, after establishing that the global means did not differ significantly across groups and conditions ($P > 0.05$). For the comparison of the seven controls to the seven Alzheimer's disease patients, differences in response (placebo/citalopram) between-groups (controls and Alzheimer's disease patients) were compared using the multigroup: conditions and covariates option in SPM99 (Aim 1). For the comparison of the PET scans sessions before and during galantamine in the Alzheimer's disease patients, the primary statistical comparisons involved (i) comparing the two placebo scans to evaluate the galantamine effect; (ii) comparing the two citalopram scans to measure the difference before and during galantamine treatment and (iii) comparing differences in the cerebral metabolic response to citalopram (citalopram–placebo) for the two conditions (baseline/galantamine; Aim 2). The between and within group comparisons were considered significant at a *t*-threshold >3.51 ($z > 2.98$, $P < 0.001$; uncorrected for multiple independent comparisons).

Results

Clinical and cognitive data

The effects of galantamine on cognition (MMSE, ADAS-COG) and behaviour (NPI) and overall clinical improvement (CBIC plus) are shown in Table 1. The effect of time for the MMSE ($F = 1.10$, df = 2.12, $P > 0.1$), ADAS-COG ($F = 1.5$, df = 2.12, $P > 0.1$) and NPI ($F = 0.18$, df = 2.12, $P > 0.1$) was not significant. The effect of time for the CBIC plus was significant ($F = 13.7$, df = 2.12,

Table 1 Clinical characteristics

	Mean ± SD		
	Baseline	2 months	6 months TX
Mini Mental Status Examination	23.3 ± 2.1	24.8 ± 4.1	23.0 ± 4.5
ADAS COG	19.3 ± 7.2	16.0 ± 8.1	18.0 ± 8.3
Neuropsychiatric Inventory (NPI)	7.71 ± 10.9	8.57 ± 7.2	5.42 ± 11.1
Clinician's Interview-Based Impression of Change plus Caregiver Input (CIBIC-plus)	7.42 ± 1.51	4.14 ± 1.34*	4.50 ± 0.54*

*Significantly different from baseline ($P < 0.01$).

$P = 0.001$). *Post hoc* testing revealed a significant difference between the two follow-up scores relative to the baseline ($P < 0.01$).

Citalopram and prolactin concentrations

Comparison of Alzheimer's disease patients to controls (Aim 1)

For the citalopram concentrations, the AUC was 6167 ± 819 for the controls and 5003 ± 1379 for the Alzheimer's disease patients. While the concentrations were higher in the controls, the difference between the groups was not statistically significant ($F = 3.68$, df = 1.13, $P > 0.05$). For the prolactin concentrations, the AUCs were as follows: Controls: placebo infusion: 1012 ± 318 and citalopram infusion 2718 ± 1885; Alzheimer's disease patients: placebo infusion: 1948 ± 1663 and citalopram infusion 2230 ± 1673. The effect of condition was significant ($F = 3.7$, df = 1, $P > 0.05$), but the effect of diagnosis ($F = 0.1$, df = 1.12, $P > 0.1$) and the condition by diagnosis interaction was not statistically significant ($F = 0.05$, df = 1.12, $P > 0.1$), even after including citalopram concentration as a covariate in the analysis ($P > 0.1$). For the individual data points for the citalopram and prolactin measures, repeated measures analysis of variance showed that the main effect of diagnosis and condition and the diagnosis by time by condition interactions were not significant ($P > 0.05$).

Galantamine Comparison in the Alzheimer's disease patients (Aim 2)

For the citalopram concentrations, the AUC was 5003 ± 1379 and 4945 ± 1915 for the pre-treatment and galantamine treatment conditions and did not differ significantly ($F = 0.01$, df = 1.6, $P > 0.1$). For the prolactin concentrations, the AUCs were as follows: Pre-treatment: placebo infusion: 1948 ± 1663 and citalopram infusion 2230 ± 1673; during galantamine treatment: placebo infusion: 1150 ± 188 and citalopram infusion 2178 ± 1941. The effects of drug ($F = 0.27$, df = 1.6, $P > 0.1$) and condition ($F = 3.46$, df = 2.19, $P > 0.1$) and the drug by condition ($F = 1.10$, df = 2.19, $P > 0.1$) interaction were not significant.

Glucose metabolism PET data

The results of the SPM analysis of the cerebral metabolic data are shown in Tables 2 and 3.

Comparison of Alzheimer's disease patients to controls (Aim 1)

The baseline comparison of resting cerebral glucose metabolism in the Alzheimer's disease patients relative to controls (data not shown) demonstrated significant metabolic reductions in right middle temporal, left posterior cingulate and parietal cortices (precuneus and inferior parietal lobule), consistent with the pattern of metabolic deficits in Alzheimer's disease shown in prior studies using voxel-based data analysis methods (Minoshima *et al*., 1997: Reiman *et al*., 2005).

The cerebral metabolic effects of citalopram in the controls (citalopram–placebo conditions) are shown in Table 2, Panel A. The cerebral metabolic effects of citalopram in the Alzheimer's disease patients (citalopram–placebo conditions) are shown in Table 3, Panel A. The comparison of the metabolic response to citalopram in Alzheimer's disease patients relative to controls (difference between citalopram–placebo conditions between groups) are shown in Table 2, Panel B. The cerebral metabolic effects of citalopram *prior to galantamine treatment* are described in the previous paragraph (and shown in Table 3, Panel A).

Galantamine Comparison in the Alzheimer's disease patients (Aim 2)

The cerebral metabolic response to citalopram during galantamine treatment (citalopram–placebo conditions) is shown in Table 3, Panel B. The effect of galantamine treatment on cerebral glucose metabolism in Alzheimer's disease (comparison of placebo conditions is shown in Table 3, Panel C. The comparison of citalopram conditions in Alzheimer's disease (during–prior to galantamine treatment) is shown in Table 3, Panel D. The areas of cerebral metabolic increased superimposed on an MR template are shown in Fig. 1.

Discussion

The results of the present study demonstrate a greater cerebral metabolic response to acute citalopram administration in Alzheimer's disease patients relative to controls (Aim 1). The citalopram concentrations were non-significantly higher in the controls than patients. While the baseline prolactin concentrations were higher in the Alzheimer's disease patients than the controls, the magnitude of increase in prolactin concentrations did not differ significantly between groups (even when covarying for the citalopram concentrations). The greater cerebral metabolic response to citalopram in the Alzheimer's disease patients, despite the lack of change in plasma prolactin concentrations, may represent a

Table 2 The cerebral metabolic response to citalopram in Alzheimer's disease and normal controls

Talairach coordinates (*x*, *y*, *z*; mm)	Region	*z*-score	Cluster size K_E[a]
Panel A. Normal controls: change in cerebral glucose metabolism between acute citalopram administration and placebo conditions			
Decrease in metabolism			
12 −22 40	Right cingulate gyrus	3.03	131
−16 48 20	Left superior frontal gyrus	4.29	237
10 −24 48	Right paracentral lobule (BA 06)	3.53	131
6 28 34	Right middle frontal gyrus (BA 06)	3.09	610
−40 8 40	Left middle frontal gyrus	4.31	1023
−38 −68 18	Left middle temporal gyrus	3.15	610
14 −58 22	Right precuneus	3.32	1210
−60 −14 30	Left post-central gyrus	3.80	1023
−6 −64 16	Left posterior cingulate	4.17	1210
−62 −42 22	Left inferior parietal lobule (BA 40)	3.30	553
−28 −70 −24	Left cerebellum	3.17	202
Increase in metabolism			
−50 −4 14	Left pre-central gyrus	4.44	831
42 14 0	Right insula (BA 13)	4.58	2140
−44 6 2	Left insula (BA 13)	4.29	831
−52 −62 −4	Left middle occipital gyrus (BA 19)	3.90	107
Panel B. Comparison of response in Alzheimer's disease patients to controls			
Greater decreases in Alzheimer's disease patients relative to controls			
42 20 52	Right superior frontal gyrus (BA 08)	3.22	3729
34 60 10	Right middle frontal gyrus (BA 10)	3.74	3729
−10 −10 56	Left middle frontal gyrus	3.39	283
−40 0 −2	Left insula	3.78	241
54 −74 26	Right middle temporal gyrus (BA 39)	2.98	1288
4 −42 40	Right posterior cingulate gyrus (BA 31)	4.00	429
34 −48 −8	Right fusiform gyrus	3.16	383
50 −60 −40	Right cerebellum	3.20	206
Greater increases in Alzheimer's disease patients relative to controls			
−30 −70 −24	Left cerebellum	3.84	293

All coordinates are significantly different at the voxel level ($P<0.001$ uncorrected).
a voxel = 8 mm^3.
BA = Brodmann Area.

compensatory process for the reduced serotonin transporter, 5-HT2A and 5-HT1A receptor densities observed in Alzheimer's disease patients shown by both neuropathological and neuroimaging methods (as reviewed by Meltzer *et al*., 1998) or to compensate for cholinergic dysfunction (Quirion *et al*., 1985; Quirion and Richard, 1987). Studies in the rat have shown compensatory changes in the serotonin system secondary to lesions of the basal forebrain cholinergic nuclei (Quirion *et al*., 1985, Quirion and Richard, 1987). Future studies should be undertaken to evaluate the mechanisms underlying the greater cerebral metabolic response to citalopram in Alzheimer's disease patients relative to controls with respect to serotonergic and cholinergic mechanisms and the relationship to cognitive deficits and vulnerability to behavioural symptoms.

With respect to the clinical effects of galantamine, there was evidence of relatively consistent cognitive performance over the 8 months of the study and global clinical improvement as evidenced by the CBIC plus during the course of galantamine treatment. The plasma citalopram concentrations and the prolactin response to citalopram were not significantly different between baseline and galantamine conditions, which indicate that the cerebral metabolic effects of citalopram before and during galantamine treatment were not attributable to differences in citalopram concentrations. In both the comparison of Alzheimer's disease patients to controls and of the Alzheimer's disease patients before and during galantamine treatment, the difference in the cerebral metabolic response was greater than the neuroendocrine prolactin response.

It is important to note that there are similarities between the functional neuroanatomic effects of acute citalopram and the pattern observed with behavioural activation paradigms, including mood induction, attention and memory tasks and during conditions of hunger and satiety (as reviewed in Fletcher *et al*., 1995; Tataranni *et al*., 1999: Liotti *et al*., 2000; Smith *et al*., 2002a, b). These are all behaviours for which a modulatory role of serotonin has been described (as reviewed by Lucki, 1998). The regions modulated by acute citalopram include the heteromodal association cortices that in part, comprise the default network that is relatively activated even when the brain is not performing a task (Mazoyer *et al*., 2001; Raichle *et al*., 2001). While acute citalopram administration does not produce a unique pattern of neuroanatomic alterations, rather a brain network is activated that is involved in many affective, cognitive and motivational functions.

Table 3 The Effects of galantamine on the cerebral metabolic response to citalopram

Talairach coordinates (*x*, *y*, *z*; mm)	Region	*z*-score	Cluster size K_E[a]
Panel A. The cerebral metabolic response to citalopram prior to galantamine treatment (citalopram-placebo conditions)			
Decrease in metabolism			
32 62 −4	Right superior frontal gyrus (BA 10)	3.16	907
34 60 8	Right middle frontal gyrus	3.38	907
−8 −10 56	Left middle frontal gyrus	3.29	126
4 −48 34	Right posterior cingulate (BA 31)	4.29	1151
−4 −72 24	Left posterior cingulate (BA 31)	3.72	1151
22 4 12	Right putamen	3.07	385
−6 −16 10	Left thalamus (medial dorsal nucleus)	3.98	197
−4 −76 −26	Left cerebellum	3.65	1681
Increase in metabolism			
−40 −42 38	Left inferior parietal lobule	3.03	147
−52 6 −10	Left superior temporal gyrus	3.01	52
Panel B. The cerebral metabolic response to citalopram during galantamine treatment (citalopram-placebo conditions)			
Decrease in metabolism			
−20 16 −18	Left inferior frontal gyrus (BA 47)	3.25	770
−10 −36 66	Left post-central gyrus	3.16	1507
Increase in metabolism			
34 38 −10	Right middle frontal gyrus	3.49	146
16 −18 56	Right middle frontal gyrus	3.21	507
56 −22 16	Right post-central gyrus	3.10	104
60 −34 6	Right superior temporal gyrus (BA 22)	3.25	168
38 −68 20	Right middle temporal gyrus	3.41	106
42 −76 −24	Right cerebellum	3.49	544
Panel C. The effects of galantamine treatment on cerebral glucose metabolism (comparison of placebo conditions)			
Decrease in metabolism			
22 18 −16	Right inferior frontal gyrus	4.39	335
52 −2 6	Right pre-central gyrus	3.37	120
Increase in metabolism			
−30 −10 −14	Left inferior frontal gyrus	3.04	641
24 −64 30	Right precuneus	4.37	462
54 −52 46	Right inferior parietal lobule (BA 40)	3.19	1261
54 −74 0	Right middle occipital gyrus (BA 19)	3.32	1261
Panel D. Comparison of citalopram conditions (during–prior to galantamine treatment)			
Decrease in metabolism			
−50 −22 12	Left middle temporal gyrus	4.42	4218
−16 6 2	Left putamen	4.14	4218
−34 −72 −24	Left cerebellum	3.18	177
Increase in metabolism			
4 28 40	Right middle frontal gyrus (BA 08)	2.98	638
−4 14 46	Left middle frontal gyrus	3.39	638
10 −24 48	Right paracentral lobule (BA 06)	3.26	667
4 −44 40	Right posterior cingulate gyrus (BA 31)	3.07	667
36 −62 −8	Right fusiform gyrus	3.74	6096

All coordinates are significantly different at the voxel level ($P < 0.001$ uncorrected).
a voxel = 8 mm^3.
BA = Brodmann Area.

The results of the cerebral metabolism data indicate that the nature of the acute cerebral metabolic effects of citalopram is different during treatment with galantamine compared with the response prior to treatment (Aim 2). As described, prior to treatment with galantamine, acute citalopram administration decreased cerebral metabolism in patients to a greater extent than controls. During galantamine treatment, citalopram increased metabolism in right anterior cortical regions (frontal and temporal cortices). Galantamine treatment was associated with an increase in metabolism in right posterior (parietal and occipital association) cortical regions compared to baseline. When considering the galantamine effect (citalopram–placebo conditions during galantamine treatment), significant increases in metabolism was observed in right frontal and parietal cortices. When comparing the two citalopram conditions (citalopram during–prior to galantamine treatment), significant increases in metabolism were observed in frontal cortices

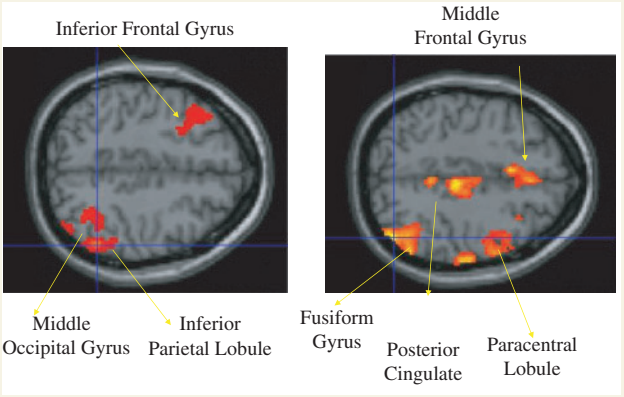

Fig. 1 Increases in cerebral metabolism with galantamine and combined galantamine/citalopram in Alzheimer's disease. The panel on the left shows the increase in cerebral metabolism with galantamine treatment in Alzheimer's disease [galantamine − baseline]. The panel on the right shows the increase in cerebral metabolism during galantamine treatment after acute citalopram administration [galantamine: citalopram-saline versus pre-treatment: citalopram-saline].

(bilaterally), as well as in posterior cingulate and occipital areas. These findings indicate that the increase in metabolism after citalopram administration during galantamine treatment is not only a function of the effect of galantamine on metabolism, but may be a synergistic effect of the two medications.

The cerebral metabolic effects of galantamine observed in the present study are similar to the metabolic effects reported in previous studies of galantamine and other cholinesterase inhibitors (Tune *et al*., 2003; Mega *et al*., 2005). Compared to the present study, previous studies have not shown an increase in metabolism in the posterior cingulate gyrus as was observed with combined cholinergic–serotonergic interventions. This region is particularly important as the posterior cingulate has been site of the earliest metabolic reductions in Alzheimer's disease (Minoshima *et al*., 1997; Reiman *et al*., 2005). With respect to the neurochemical mechanisms underlying the present findings, it is important to note that the results obtained with galantamine may be attributable to either the cholinesterase inhibition or nicotinic receptor modulation mechanisms of the drug or both, in addition to secondary neurochemical effects on other neurotransmitter systems such as dopamine (Harvey *et al*., 1995), which would have affected both the prolactin and metabolic data. As glucose metabolic activity represents the final common pathway of neurochemical activity in the brain, the data represent the functional neuroanatomic alterations associated with the pharmacologic interventions. The evaluation of the regional pattern of change may suggests which neurochemical pathways mechanisms may be involved. In the present study, the cerebral metabolic alterations observed are in cortico–cortico pathways for which glutamate is the primary neurotransmitter (Fagg and Foster, 1983). In addition, a glutamatergic mechanism may be involved in the cerebral metabolic deficits observed in Alzheimer's disease (Smith *et al*., 1992). As both citalopram and galantamine have been shown to affect glutamate neurotransmission, consistent with a modulatory role of serotonin and acetylcholine (Golembiowska and Dziubina, 2000; Takada-Takatori *et al*., 2006), the metabolic alterations observed may represent a secondary, synergistic effect of cholinergic and serotonergic agents on the glutamate system.

Several limitations of the present study should be considered in interpreting the results. In the study design, a group of Alzheimer's disease patients scanned on two occasions without cholinesterase inhibitor treatment was not included. Given the long duration of treatment, it would not have been feasible to identify Alzheimer's disease patients who were not willing to take cholinesterase inhibitors over the time interval of study. Second, as described in the Materials and Methods Section, the Alzheimer's disease patients did show evidence of behavioural symptoms as assessed by the NPI (e.g. apathy, depression, anxiety, agitation), but did not meet criteria for an axis I DSM IV psychiatric diagnosis. It is possible that the behavioural symptoms may have introduced variability in the glucose metabolism data as has been shown in previous studies (Lopez *et al*., 2001a, b), as well as in the response to serotonergic or cholinergic agents. Given the natural history of Alzheimer's disease, it would be difficult to identify subjects free of neuropsychiatric symptoms. Thirdly, the issue of the variability of the data and the small sample size should be considered. The sample size is small because only patients who had not been treated previously with cholinesterase inhibitors were enrolled and such patients are difficult to identify as the majority of patients are treated. The pattern of results and direction of the effects are consistent with the study hypothesis based on previous glucose metabolism studies with acute citalopram and cholinesterase inhibitors (separately) and with preclinical data. With respect to the citalopram and prolactin concentrations, the standard deviations for the measurements are large, but are not explained by intra-assay variability as discussed in the Materials and methods section. In reviewing the data for the individual time points (as shown in the Supplementary material), the variability lies in the magnitude of the peak effects. For the time points other than the peak citalopram concentrations and prolactin effect, the variability observed is consistent with the precision of the measurements. Thus, during the time of maximal increase in citalopram and prolactin concentrations, the magnitude of response was variable across subjects. With respect to the cerebral metabolism data, the data for the significant voxels were evaluated to determine the degree of between subject variability in response. Representative plots for the posterior cingulate gyrus for two of the contrasts (placebo versus citalopram prior to treatment and citalopram during treatment versus pre-treatment) are provided in the Supplementary material. In both cases, the direction of the effects between subjects is relatively consistent, although the magnitude change differs between subjects. Thus, even though the sample size is small, the direction of the metabolic effects is relatively consistent. Using the same acute citalopram paradigm in geriatric depressed patients with a similar sample size, the results of a study of six patients and the results of a larger group of 16 patients were similar (Smith *et al*., 2002a, b, 2008). Thus, despite the small sample size, the findings are comparable to or less variable, given the variability typically observed in neuroimaging studies.

The significance of acute citalopram administration relative to the clinical use of citalopram on a chronic basis should be considered. Acute citalopram administration is intended as a 'challenge' to measure the consequences of an acute increase in serotonin concentrations on cerebral metabolism. Acute citalopram administration (as in the present study) is associated with 70% serotonin transporter occupancy, which is comparable with the magnitude of blockade observed with chronic citalopram treatment (Hinz *et al*., 2008). While there is a neurochemical effect of acute citalopram with respect to occupancy of the initial site of action and increases in extracellular serotonin (Kreiss *et al*., 1993), the clinical antidepressant effect in depressed patients is not observed until after chronic administration. In comparing the chronic to acute effects of citalopram in geriatric depressed patients, similar changes in metabolism are observed, in addition to alterations in other regions (e.g. putamen, parahippocampal gyrus and amygdala) and the effects tend to be bilateral rather than unilateral (Smith *et al*., 2002a, b). Studies in geriatric depressed patients have shown that greater magnitude of acute cerebral metabolic response to citalopram is associated with greater improvement of depressive symptoms after a 12-week clinical trial of citalopram (Smith *et al*., 2008). Thus, these data suggest that acute cerebral metabolic response of to citalopram may reflects the capacity of the brain to respond to chronic antidepressant treatment. With respect to the present study, the cerebral metabolic response to acute citalopram in Alzheimer's disease is greater in patients than controls. This metabolic response may represent a compensatory process secondary to the substantial loss of serotonin transporter and receptors in Alzheimer's disease. As the brain demonstrates a capacity to respond to acute citalopram in Alzheimer's disease, this may suggest why there is a synergic metabolic effect of combined interventions. Similar to the depression data, the capacity of the brain to respond may be related to clinical and metabolic outcomes. This may also suggest why chronic serotonergic interventions have been effective in Alzheimer's disease and why combined chronic, serotonergic–cholinergic treatments may be an effective therapeutic strategy. Such a study of chronic treatment with both agents, would be a logical next step for the research.

In contrast to studies of serotonin transporters and receptors in Alzheimer's disease, the present study provides evidence for an altered dynamic response of the brain to an acute pharmacologic increase in serotonin, as well as a synergistic effect of serotonergic and cholinergic interventions, consistent with preclinical studies of interactions between the two neurotransmitter systems. The present study provides preliminary support for a synergistic effect of acute SSRI administration and cholinesterase inhibitor treatment on cerebral metabolism in Alzheimer's disease. Several lines of preclinical and clinical evidence support further investigations of the neurobiological effects of combined chronic treatment with the two classes of agents. With respect to the SSRI's, the evidence of a neurotrophic effect of SSRI's, as well as recent evidence of a prophylactic effect of SSRI's in animal models of Alzheimer's disease had led to the suggestion that chronic use of the SSRI in neurodegenerative disease may improve function and slow disease progression (Duman, 1998, Nelson *et al*., 2007). Thus, data in animals suggest that a greater clinical benefit may be achieved by combined treatment. With respect to clinical studies, the results of several double blind, placebo controlled studies indicate that addition of an SSRI to a cholinesterase inhibitor produced greater functional improvement in Alzheimer's disease patients compared with cholinesterase inhibitor treatment alone (Finkel *et al*., 2004). SSRIs have been shown to be effective in treating depression secondary to Alzheimer's disease, which may also improve function (Lyketsos *et al*., 2003). The observations from clinical studies of combined SSRI and cholinesterase inhibitor treatment, considered with the preliminary neuroimaging data suggest that future studies should be undertaken to further evaluate the cognitive and neurobiological consequences of chronic, combined cholinergic and serotonin interventions in Alzheimer's disease.

Supplementary material

Supplementary material is available at *Brain* online.

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